Limitations of End-Tidal CO_2 as an Early Indicator of Central Hypovolemia in Humans

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Abstract

Objective. This study tested the hypothesis that pulmonary end-tidal CO_2 ($PETCO_2$) tracks reductions in central blood volume in human volunteers exposed to progressive central hypovolemia. **Methods.** Measurements of $PETCO_2$, systolic (SBP), diastolic (DBP), and mean arterial (MAP) blood pressures, heart rate (HR), stroke volume (SV), and respiratory rate (RR) were obtained in 50 healthy human subjects during baseline supine rest and exposure to progressive reductions of central blood volume produced by application of lower body negative pressure (LBNP). **Results.** As increasing amounts of LBNP were applied, SBP, DBP, MAP, HR, SV, and $PETCO_2$ decreased ($p < 0.001$). RR was not altered ($p = 1.0$). The decrease in $PETCO_2$ did not begin to occur until 40% of maximal LBNP was applied. While $PETCO_2$ decreased progressively thereafter, the range of baseline values (28.8–49.2 mmHg) varied more than the reduction in $PETCO_2$ elicited by maximal LBNP (baseline = 40.1 ± 0.6 mmHg; maximal LBNP = 29.8 ± 1.0 mmHg). The earliest significant alteration was observed in SV, which occurred at 20% of maximal LBNP. MAP did not decline significantly until 80% of maximal LBNP was reached. $PETCO_2$ was correlated positively with SV ($r^2 = 0.87$).**Conclusions.** Although $PETCO_2$tracked decreases in SV in this human model of progressive central hypovolemia, reductions in $PETCO_2$were small relative to the range of baseline values. Thus, monitoring such small reductions in $PETCO_2$ as an early warning of imminent cardiovascular collapse during hemorrhage may not be clinically useful without monitors capable of providing continuous trending.
Key words: hemorrhagic shock; lower body negative pressure; cardiovascular collapse

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Introduction

Hemorrhage resulting from traumatic injuries is the leading cause of preventable mortality in both the civilian and military settings, and is responsible for up to 80% of civilian trauma deaths and 50% of combat-related deaths.[1,2] Many of these trauma deaths may be preventable if the severity of blood loss is recognized in the prehospital setting.[3,4] Thus, new approaches for early detection of blood loss in prehospital and combat environments continue to be sought in both the civilian and military trauma sectors.

Several criteria have been advocated to determine injury severity, mode of transport, priorities of treatment, and patient destination for the triage of trauma patients.[5–12] However, most of these existing triage tools currently utilize the patients' standard vital-sign data because of the assumption that these measurements are readily obtainable at the site of injury and will provide a "snapshot" of patient stability. Such an assumption is problematic because of the dynamic physiology of the hemorrhaging trauma patient. During early volume loss, reflex cardiovascular and neurohormonal mechanisms act to maintain normal arterial pressures with only mild tachycardia. Specifically, autonomically mediated reflexes initiate strong sympathetic responses that result in intense vasoconstriction and help defend against severe hypotension. Thus, the use of standard vital signs may not truly reflect the degree of blood-volume loss and, subsequently, may not provide early decision support for recognition of the severity of injury. Therefore, the current process and practice of prehospital trauma care may be significantly improved by providing appropriate noninvasive, advanced, or continuous physiologic observations that are better early indicators of blood-volume loss and impending circulatory collapse.

One such proposed noninvasive indicator is continuous pulmonary end-tidal CO_2 ($PETCO_2$), which is currently used in the prehospital setting to evaluate mechanical ventilation, assess endotracheal tube placement, and determine adequacy of resuscitation.[13] Previous studies have shown $PETCO_2$ to correlate with cardiac output in both animal and human models experiencing cardiogenic and hemorrhagic shock.[14–17] However, most of these studies focus on $PETCO_2$measurements during low-flow states or when assessing adequacy of resuscitation.[18,19] One animal study revealed that $PETCO_2$ decreased within 30 minutes of hemorrhagic shock, but a possible link between changes in $PETCO_2$ and early hemorrhagic states in humans has not been investigated.[20]

The investigation of $PETCO_2$ as a potential early indicator of hemorrhagic status has been limited by 1) the absence of continuous trending capabilities for standard medical monitoring of trauma patients and 2) the ethical restrictions of withdrawing large amounts of

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blood from healthy human subjects (i.e., experimentally induced hemorrhage). We addressed the latter challenge by using lower body negative pressure (LBNP) as a method for the progressive reduction in central blood volume, since LBNP has been shown to mimic the acute hemodynamic and autonomic responses associated with actual hemorrhage.[21–23] In the present investigation, we compared $PETCO_2$, heart rate, arterial pressures, and stroke volume at rest and during graded exposure to LBNP to test the hypothesis that $PETCO_2$ directly correlates with reductions in central blood volume in humans exposed to a noninvasive model of central hypovolemia.

MATERIALS AND METHODS

Subjects

Fifty healthy nonsmoking subjects (29 males, 21 females) with mean ± standard deviation (SD) age of 30 ± 9 years, body weight of 75 ± 15 kg, and height of 173 ± 10 cm were recruited to participate. A complete medical history and physical examination were obtained on each of the potential subjects. In addition, female subjects underwent an initial urine test prior to experimentation to ensure that they were not pregnant. Subjects maintained their normal sleep pattern, refrained from exercise, and abstained from caffeine and other autonomic stimulants, such as prescription or nonprescription drugs, for at least 24 hours prior to each experimental protocol, unless cleared by the physician medical screener to continue taking the medications.

During an orientation session that preceded each experiment, all subjects received a verbal briefing and a written description of all procedures and risks associated with the experiments, and were made familiar with the laboratory, the protocol, and procedures. Experimental procedures and protocols were reviewed and approved by the Institutional Review Board for the use of human subjects at the Brooke Army Medical Center at Fort Sam Houston, Texas. Each subject gave written, informed, voluntary consent to participate in the experiments.

Model of Central Hypovolemia

LBNP was used in the present investigation as an experimental tool to simulate loss of central blood volume (e.g., hemorrhage) in humans.[21,23] With the use of a neoprene skirt designed to form an airtight seal between the subject and the chamber, the application of negative pressure to the lower body (below the iliac crest) with the subject in a supine position results in a redistribution of blood away from the upper body (i.e., head and heart) to the lower extremities and abdomen (Figure 1A). Thus, this model provides a unique method of investigating conditions of controlled, progressive, experimentally induced hypovolemic hypotension. Absolute equivalence between the magnitude of negative pressure applied and the magnitude of actual blood loss cannot, at this time, be determined, but review of both human and animal data reveal ranges of effective blood loss (or fluid displacement) caused by LBNP.[21] Based on the magnitude of central hypovolemia, we have previously proposed that 10–20 mmHg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss ranging from 400 to 550 mL; 20–40 mmHg negative pressure equates to blood loss ranging from 550 to 1000 mL; and greater than 40 mmHg negative pressure induces hemodynamic responses that are equivalent to those resulting from blood loss approximating 1000 mL or more.[21]

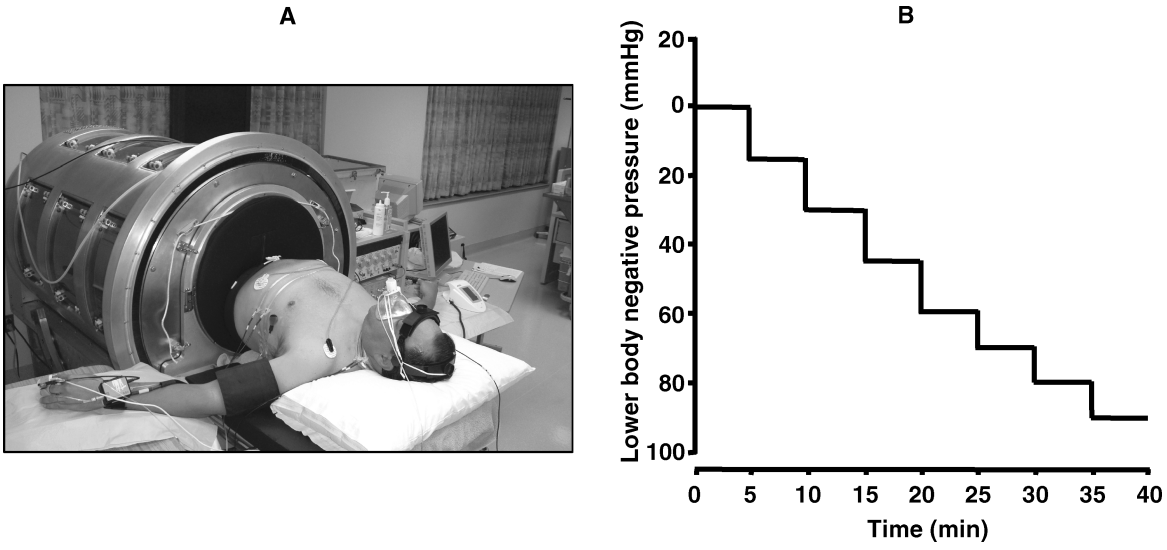

FIGURE 1. Subject in the lower body negative pressure (LBNP) device showing measurement of end-tidal CO_2 via sidestream (**A**), and a schematic representation of the LBNP protocol (**B**).

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Experimental Protocol

All subjects were instrumented with an infrared finger photoplethysmograph (Finometer® Blood Pressure Monitor; TNO-TPD Biomedical Instrumentation, Amsterdam, The Netherlands) and an electrocardiogram to record beat-by-beat arterial pressures and pulse rate. The Finometer blood pressure cuff was placed on the middle finger of the left hand which, in turn, was laid at heart level. Excellent estimates of directly measured intra-arterial pressures during various physiological maneuvers have been demonstrated with this device.[24–26] Mean arterial pressure (MAP) was calculated by dividing the sum of systolic blood pressure (SBP) and twice diastolic blood pressure (DBP) by three. Pulse pressure (PP) was calculated by subtracting DBP from SBP. $PETCO_2$ was monitored on a breath-by-breath basis as subjects exhaled into a face mask (BCI Capnocheck Plus; Smiths Medical Inc., Waukesha, WI).

Beat-to-beat stroke volume (SV) was measured noninvasively, using thoracic electrical bioimpedance, with an HIC-2000 Bio-Electric Impedance Cardiograph (Bio-Impedance Technology, Chapel Hill, NC). The thoracic electrical bioimpedance technique is based on the resistance changes in the thorax to a low-intensity (4 mA), high-frequency (70 kHz) alternating current applied to the thorax by two surface electrodes placed at the root of the neck and two surface electrodes placed at the xiphoid process at the midaxillary line. Ventricular SV was determined with the partly empirical formula: $SV \text{ (in mL)} = \rho \times (L/Z_0)^2 \times LVET \times (dZ/dt)$, where ρ (in ohm/cm) is the blood resistivity, a constant of 135 ohms/cm *in vivo*; L (in cm) is the mean distance between the inner-band electrodes (front and back); Z_0 (in ohms) is the average thoracic background impedance; LVET (in seconds) is the left ventricular ejection time; and (dZ/dt) is the maximum height of the dZ/dt peak measured from the zero line.[27] Correlation coefficients of 0.70–0.93 have been reported in SV measurements simultaneously made with thoracic electrical bioimpedance and thermodilution techniques.[28]

Each subject underwent exposure to an LBNP protocol designed to test their tolerance to experimentally induced hypotensive hypovolemia. The LBNP protocol consisted of a five-minute rest period (0 mmHg), followed by five minutes of chamber decompression to −15, −30, −45, and −60 mmHg, and additional increments of −10 mmHg every five minutes until the onset of cardiovascular collapse or the completion of five minutes at −100 mmHg (Fig. 1B). Cardiovascular collapse was defined by one or a combination of the following criteria: 1) a precipitous fall in SBP greater than 15 mmHg; 2) a sudden decrease in HR > 15 bpm; 3) progressive diminution of SBP below 70 mmHg; and/or 4) voluntary subject termination due to onset of presyncopal symptoms such as grey-out (loss of vision), sweating, nausea, or dizziness.

Outcome Measures

The primary outcome measure was $PETCO_2$. Secondary outcome measures were SBP, DBP, MAP, PP, SV, HR, and respiratory rate (RR).

Statistical Analysis

Subjects reached cardiovascular collapse (i.e., maximal LBNP tolerance) at different absolute LBNP levels, based on their individual physiological responses. Because these responses are the same at cardiovascular collapse independent of the LBNP level at which an individual subject reaches this point,[29] we chose to normalize each individual's data by reapportioning their responses to equal fractions between 0% LBNP tolerance (baseline) and 100% LBNP tolerance, the level at which the LBNP protocol was terminated as a result of impending cardiovascular collapse (presyncope). This approach allowed us to consider the data from all subjects relative to their maximum capacity for LBNP tolerance.

Cardiovascular variables were averaged over the last three minutes of each LBNP level. A one-way (LBNP level) randomized block (subjects) analysis of variance for repeated measures was used for comparison of outcome variables. If statistical differences were found, Bonferroni-corrected comparisons with baseline measurements were performed to determine the first level of LBNP that could be distinguished statistically from baseline. Linear regression analysis was used as appropriate to correlate changes in variables. All data are presented as mean ± SD and exact p-values are presented for all comparisons.

Results

The mean values at baseline and 100% LBNP tolerance for all variables are displayed in Table 1. All outcome variables exhibited statistically significant alterations between baseline and presyncope (100% LBNP tolerance), with the exception of RR. Subjects

Table 1. Absolute Values of Measured Variables at Baseline and at 100% LBNP Tolerance

	Baseline	100% LBNP Tolerance	p-value
Systolic blood pressure (mmHg)	136 ± 11	104 ± 18	<0.001
Diastolic blood pressure (mmHg)	78 ± 6	73 ± 10	<0.001
Mean arterial pressure (mmHg)	101 ± 7	84 ± 11	<0.001
Pulse pressure (mmHg)	58 ± 10	30 ± 10	<0.001
Heart rate (beats/minute)	65 ± 11	115 ± 23	<0.001
Stroke volume (mL)	149 ± 39	57 ± 22	<0.001
Respiratory rate (breaths/minute)	15 ± 4	15 ± 4	0.972
End-tidal CO_2 (mmHg)	40.1 ± 4.3	29.8 ± 6.6	<0.001

All data are presented as mean ± SD.

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exhibited a range of LBNP tolerance from 1185 seconds (i.e., presyncope during LBNP = −45 mmHg) to 2388 seconds (i.e., presyncope during LBNP = –90 mmHg), with a mean time to presyncope of 1809 ± 355 seconds.

Figure 2 graphically depicts SV, $PETCO_2$, MAP, and PP during LBNP. SV demonstrated a near linear decrease during LBNP, reaching statistical significance ($p = 0.004$) at only 20% maximal LBNP. PP also decreased during LBNP, with significant reductions at levels at ($p < 0.001$) and above 40% LBNP tolerance. Similarly, $PETCO_2$ was reduced ($p = 0.014$) at 40% maximal LBNP. Of note, the range of baseline $PETCO_2$ across the healthy human subjects was 28.8 to 49.2 mmHg; the total reduction in $PETCO_2$ induced by LBNP was 10.3 ± 6.4 mmHg (baseline = 40.1 ± 4.2 mmHg; maximal LBNP = 29.8 ± 6.6 mmHg), which falls within the range of baseline $PETCO_2$ values. MAP did not decline significantly until 80% LBNP tolerance ($p < 0.001$).

Figure 3 graphically depicts the amalgamated correlation between the change in $PETCO_2$ and change in SV ($r^2 = 0.87$). There was a direct linear relationship between the decreases in SV and $PETCO_2$ during LBNP, such that central hypovolemia was associated with reductions in $PETCO_2$.

DISCUSSION

There are two primary findings of this study. First, in support of our hypothesis, $PETCO_2$ indeed decreased in proportion to progressive central hypovolemia induced by LBNP in healthy human volunteers. Second, the interindividual range of baseline $PETCO_2$ values in these healthy subjects was greater than the decrease in $PETCO_2$ induced by LBNP. These data suggest that the clinical usefulness of $PETCO_2$ measurement for the assessment of central hypovolemia may be limited to situations in which continuous measurement is available

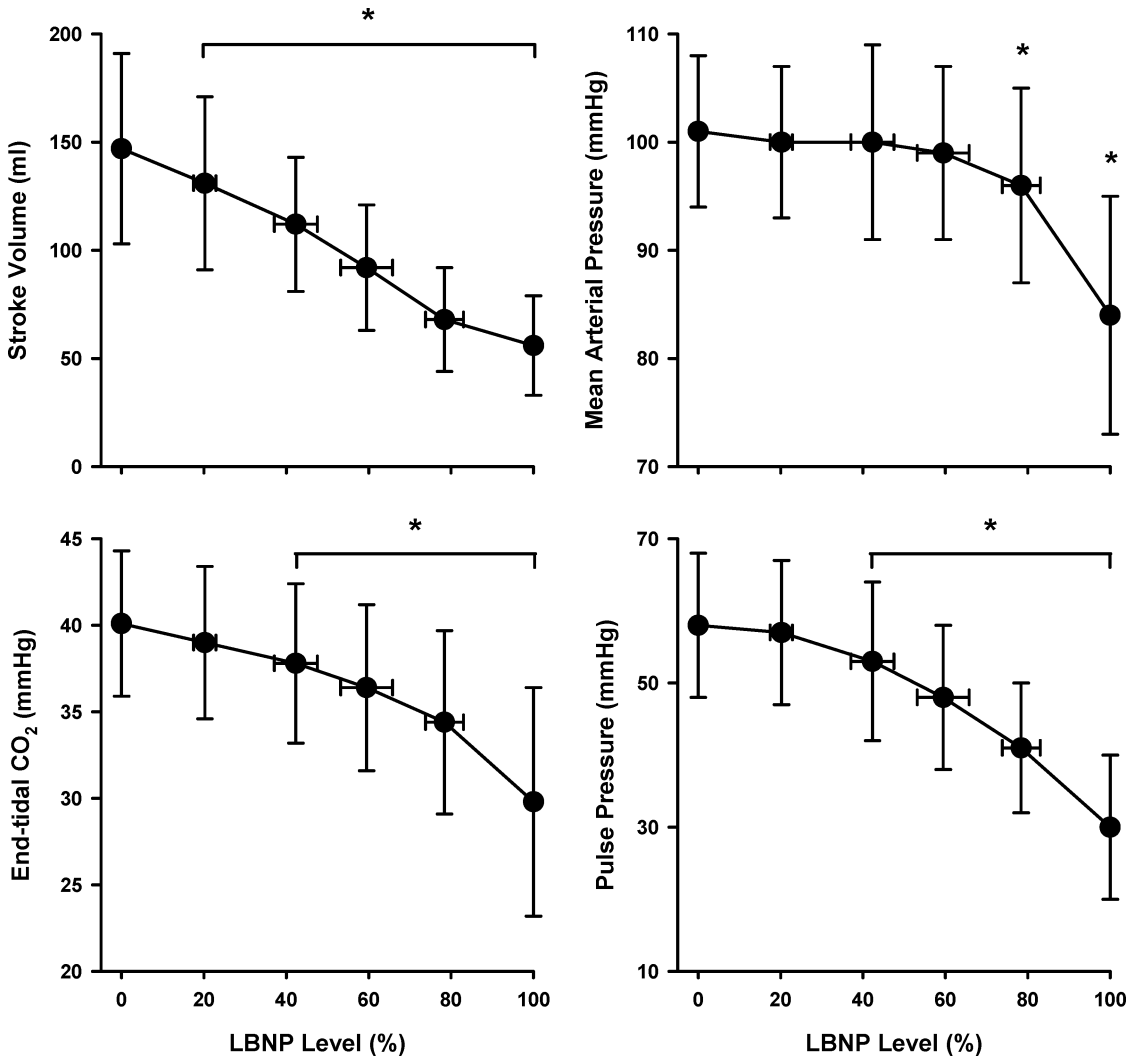

FIGURE 2. Stroke volume, mean arterial pressure, end-tidal CO_2, and pulse pressure throughout the lower body negative pressure (LBNP) protocol. Due to intersubject variation in LBNP time to cardiovascular collapse, responses to LBNP were reapportioned to equal fractions between 0% LBNP tolerance (baseline) and 100% LBNP tolerance, the level where cardiovascular collapse occurred and the LBNP protocol was stopped. Data are presented as the mean ± SD. *Denotes $p \leq 0.014$.

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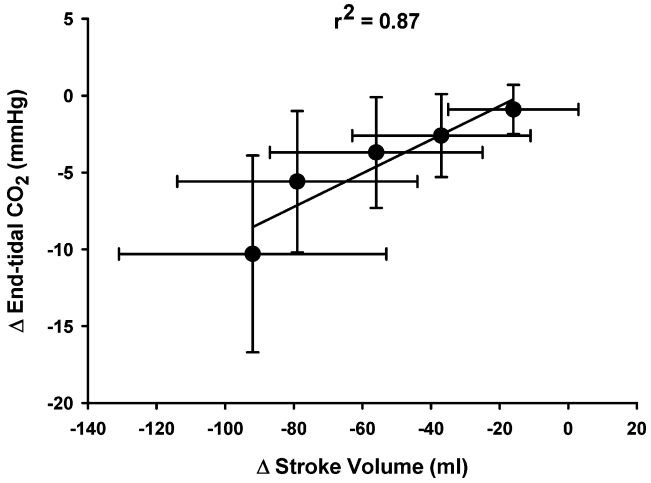

FIGURE 3. Changes in end-tidal CO_2 plotted against changes in stroke volume during the lower body negative pressure protocol. Data are presented as the mean ± SD.

within a given individual, in order that trends over time might be observed.

Several studies have demonstrated the utility of $PETCO_2$ measurements in a variety of settings related to cardiac output and changes in total blood volume.[14–17,30] $PETCO_2$ values during emergency trauma surgery have been shown to help to predict patient outcomes and can be used to help identify patients needing more aggressive resuscitation procedures.[31] $PETCO_2$ also has been shown to decrease upon standing, due to the concomitant transient decrease in cardiac output.[32] Further, $PETCO_2$ has been demonstrated to predict unclamping hypotension in patients undergoing infrarenal aortic abdominal aneurysm repair; when the aortic clamp was released, systolic hypotension (> 20%) occurred in subjects who had a decrease in $PETCO_2$ greater than 15% during aortic cross-clamping.[33] Sidestream $PETCO_2$ has been correlated with arterial PCO_2 both in the laboratory[34]and in the ED setting.[35,36]Additionally, $PETCO_2$ has been useful as a marker that reflects impaired cardiac output response to exercise in patients with a diagnosis of heart failure.[37] Buccal, sublingual, and esophageal capnometry are also being investigated to assess the severity of hemorrhagic shock and the adequacy of resuscitation.[38–42] Such findings led us to investigate $PETCO_2$ as a possible marker for blood loss.

In this study, we found that $PETCO_2$ correlated with blood loss but did not indicate central hypovolemia in humans as early as SV. However, changes in $PETCO_2$linearly tracked changes in SV (e.g., central blood volume) and proved to be an earlier indication of central hypovolemia than vital signs (e.g., heart rate, blood pressures) currently provided by standard medical monitor measurements. Perhaps the most limiting factor in using $PETCO_2$ for tracking changes in central blood volume is that individual baseline variations in $PETCO_2$ were greater than the overall delta between the baseline mean and 100% LBNP tolerance mean $PETCO_2$ values. This significant variability in baseline $PETCO_2$indicates that discrete measurement of $PETCO_2$ (i.e., a "snapshot" in time) will not be a sensitive early marker for acute hemorrhage. However, our data support the notion that medical monitors designed to assess trends in $PETCO_2$ by providing continuous measurements in individual patients may prove clinically useful for the early indication of progressive hypovolemia.

Previous work using this model of progressive central hypovolemia has demonstrated that MAP is maintained during the early stages of LBNP, despite marked reductions in SV.[43] In this initial study (n = 13), PP was found to linearly decrease with SV, suggesting that it might be an earlier indicator of volume loss. Our current findings extend these observations of MAP and PP to 50 subjects, with similar results. That is, PP decreased much earlier (at the 40% LBNP tolerance level) than MAP, which only decreased at the 80% LBNP tolerance level. This result is not surprising, as MAP is a regulated variable that is maintained by activation of autonomic compensatory mechanisms.[21] It is therefore apparent that addition of PP to currently measured standard vital signs, such as MAP, should provide more information as to the underlying physiological status of a hemorrhaging patient. This has recently been found to be the case, as prehospital measurement of arterial blood pressure could not distinguish between those trauma patients who subsequently lived and those who died.[44] Despite the similarity in arterial blood pressures at this early time point, PP was lower in those patients who eventually died.[44] Taken together, the data accrued from both our controlled laboratory model of central hypovolemia and from actual trauma patients provide strong evidence that PP allows for early, noninvasive identification of volume loss and may therefore prove a more accurate and timely triage tool than measurement of mean arterial blood pressure alone.

Limitations

There are a few limitations in this study worthy of discussion. First, our laboratory model of progressive central hypovolemia provides an unequaled opportunity to monitor real-time, continuous data on changes in key physiologic variables, but we recognize that cardiovascular responses to experimentally induced central hypovolemia may be different when compared with physiologic responses to actual severe hemorrhage. Although LBNP causes fluid redistribution from the upper to lower body instead of inducing actual blood loss, previous trials have demonstrated that many of the physiological responses to LBNP are identical to those of actual volume loss.[21,45,46] The laboratory induction

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of controlled central hypovolemia may also be seen as a benefit, inasmuch as it allows the determination of the relationship between $PETCO_2$ and reduced central volume without confounding factors, such as tissue injury and painful stimuli, that might affect respiratory drive. Thus, these results may be the first to strictly reflect this relationship in human subjects. Second, it is worthwhile to note that the sidestream method of monitoring $PETCO_2$ was used, which some studies have demonstrated to be slightly less accurate than the mainstream method of monitoring $PETCO_2$.[47] However, the mainstream method is less practical for use in the prehospital and emergency setting, as it necessitates that the patient be intubated. Finally, measuring SV using bioimpedance cardiography is an indirect method. Although we observed the expected progressive, linear reductions of SV with LBNP, we stress that the actual volume of fluid displaced was not determined.

CONCLUSIONS

$PETCO_2$measurements correlate with reductions in SV induced by LBNP in healthy humans. However, the use of changes (i.e., trending) rather than absolute values of $PETCO_2$may be more useful, since individual variation in baseline $PETCO_2$ is greater than the acute change in $PETCO_2$ induced by profound central hypovolemia in this model.

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